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"What's past is prologue": the saga of percutaneous coronary intervention

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Drug-eluting stents (DES) were conceived to reduce in-stent neointimal formation, minimising the occurrence of restenosis. Their development was pioneered through a combination of the increased understanding of the biology of restenosis, the selection of drugs that target one or more pathways in the restenotic process, controlled-release drug delivery strategies, and the use of the stent as a delivery platform.

The first successful DES programme, the CYPHER® sirolimus-eluting stent (Cordis Corporation, Johnson & Johnson, Warren, NJ, USA), was initiated in our centre in São Paulo, Brazil. Between December 1999 and January 2000, 30 patients were enrolled in the sirolimus-eluting FIM trial and received the moderate (n=15) and slow-release (n=15) formulations of this device. Four months later, in only two days, we performed the follow-up of both cohorts, with quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) evaluation[1]. At that moment, with no sophisticated study design (not even a control group!), we were sure we were looking at a new technology which would revolutionise the interventional coronary field, as was later confirmed in hundreds of randomised clinical trials and "real-world" registries[2-4].

In parallel to the broad incorporation of such devices into clinical practice, reports of new varieties of adverse events, such as very late stent restenosis and thrombosis, started to appear, raising concerns about the durability and long-term safety of the first generation of DES[5-9].

In the current edition of the AsiaIntervention Journal, Kuramitsu et al[10] present the very long-term results of their "real-world experience" with the CYPHER DES, including 985 consecutive patients

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(1,307 lesions) treated solely with this device. The authors should be congratulated for their meticulous scientific work. Important observations can be derived from their experience.

First, invasive follow-up with angiography was obtained in 88% of the total cohort. Although currently routine repeat angiography is not recommended for the majority of patients treated with PCI, at the time of the recruitment (more than a decade ago!) little was known about the performance of that novel technology in complex scenarios, which explains the interest of our colleagues in obtaining this valuable information. We did the same with the first patients treated with CYPHER, who generously agreed to undergo

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angiography at 4, 12, 24 and 48 months[1,11-13]. On the other hand, this systematic approach of routine invasive follow-up, combined with the high complexity angiographic profile enrolled in their registry (including bifurcations, coronary total occlusions, previous ISR, left main stem, etc.), might explain the relatively high target lesion restenosis (TLR) rates described in this publication (11.8% within the first year). Most of the "real-world" publications, including our local DESIRE registry[14], pointed to a single digit TLR rate within 12 months of the procedure. Of note, due to the systematic invasive follow-up, the authors were able to identify stent fracture as one of the main determinants of CYPHER failure.

A recurrent criticism in the interventional cardiology field is that the results of studies are limited to midterm follow-up. In the present manuscript, our Japanese colleagues have shown that it is possible to deliver high-quality, very long-term clinical data (median of 8.6 years). Among their main observations, the authors observed a continuous growth in target lesion revascularisation after the first year of the PCI (2.2%/year) as well as in the incidence of definitive very late stent thrombosis (0.22%/year). The incidence of these events was not tempered by the years, still occurring up to ten years after the index procedure. Although many other registries have been able to demonstrate the steady increase in thrombosis and restenosis of first-generation DES after one year of their deployment, most of them have their follow-up limited to five years. Again, we think it is interesting to establish a parallel to our DESIRE registry, in São Paulo. Our registry, currently with close to 7,000 patients, was initiated in May 2002 and has successfully clinically followed 98.2% of the entire population treated with DES (first- and second-generation) in a single-centre tertiary institution (Hospital do Coração, São Paulo, Brazil). As in the present study, we observed a continual increase in the occurrence of DES thrombosis and TLR of 0.3%/year and 1.6%/year, respectively, after the first year of the procedure, with cases happening after the first decade of the PCI. Likewise, the predictors of MACE varied according to the time point. In **Table 1**, we present the independent MACE predictors in the DESIRE registry.

It is important to highlight that, despite these untoward events experienced with the first generation of DES, these devices were instrumental in positioning PCI where it is nowadays - the preferred revascularisation strategy for the majority of patients with coronary artery disease. Also, the drawbacks observed with those devices were necessary to prompt the development of a next generation of DES, combining thinner and more flexible platforms made of new alloys (cobalt-chromium, platinum chromium, etc.), more biocompatible (e.g., fluoro polymer, phosphorylcholine, etc.) or even absorbable polymers (PLLA, PGLA, etc.) and novel antiproliferative agents (mostly sirolimus analogues or derivatives) or reduced doses of currently approved antiproliferative drugs.

The efficacy and long-term safety achieved with the current new generation of DES systems are very high and difficult to surpass; therefore, we believe that PCI will continue to play a pivotal role in the treatment of coronary artery disease. The current focus on metallic DES research is based on the development of technologies to promote faster and safer vessel healing, allowing the shortening of dual antiplatelet therapy and therefore minimising the bleeding risks associated with these medications.

Table 1. Independent predictors of acute, mid and very long-term MACE (cardiac death, non-fatal myocardial infarct and ischaemia-driven target lesion revascularisation) in the DESIRE registry.

Acute DES performance (in-hospital phase)			
Variable	**HR**	**95% CI**	***p*-value**
Stent length	1.02	1.020-1.028	<0.001
Age	1.02	1.01-1.04	<0.001
Residual stenosis	1.04	1.01-1.06	0.003
Use of first-generation DES	1.45	1.15-1.84	0.002
Treatment of SVG lesions	1.82	1.29-2.56	0.001
Midterm DES performance (>hospital discharge <365 days)			
Variable	**HR**	**95% CI**	***p*-value**
Age	1.02	1.0-1.02	0.04
Residual stenosis	1.02	1.0-1.04	0.04
Stent length	1.86	1.29-2.67	0.01
Smoking	1.98	1.31-2.97	0.01
Treatment of SVG lesions	3.0	1.86-4.86	<0.001
Very long-term DES performance (>365 days [up to 13 years, median of 7.2 years])			
Variable	**HR**	**95% CI**	***p*-value**
Age	1.01	1.0-1.03	0.004
Residual stenosis	1.02	1.0-1.04	0.009
Stent length	1.23	1.1-1.48	<0.001
Smoking	1.46	1.4-1.9	0.003
Previous CABG	1.54	1.12-2.11	0.007
Renal insufficiency	1.66	1.18-2.31	0.003
ACS	1.72	1.28-2.30	<0.001
Treatment of SVG	1.87	1.3-2.7	0.001
Use of second-generation DES	0.77	0.58-0.99	0.04

ACS: acute coronary syndrome; CABG: coronary artery bypass graft; CI: confidence interval; DES: drug-eluting stent; HR: hazard ratio; SVG: saphenous vein graft

Conflict of interest statement

The authors have no conflicts of interest to declare.

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